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DETAILED ACTION

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

MAILED

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GROUP 1600

Application Number: 10/026,393
Filing Date: December 21, 2001
Appellant(s): QUIRK ET al

Jason Johnston
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed April 16, 2007 appealing from the Office action mailed June 9, 2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The Appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The Appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

The American Heritage Dictionary of the English Language, William Morris, Ed., 1980, Houghton Mifflin Co., Boston, MA, p. 240.

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Armstrong et al, The role of matrix metalloproteinases in wound healing. J Am Podiatr Med Assoc. 2002 Jan;92(1):12-8. Review.

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Brew et al, Tissue inhibitors of metalloproteinases: evolution, structure and function. Biochim Biophys Acta. 2000 Mar 7;1477(1-2):267-83. Review.

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Englert et al Layered expression scanning: rapid molecular profiling of tumor samples. Cancer Res. 2000 Mar 15;60(6):1526-30.

Frantz, R. A., PhD, RN, FAAN, CWCN, Professor of Nursing, College of Nursing, The University of Iowa, Chronic Wound Healing, http://www.nursing.uiowa.edu/sites/chronicwound/.

Golub et al, A matrix metalloproteinase inhibitor reduces bone-type collagen degradation fragments and specific collagenases in gingival crevicular fluid during adult periodontitis. Inflamm Res. 1997 Aug;46(8):310-9.

Graber et al Role of interactions between integrins and extracellular matrix components in healthy epithelial tissue and establishment of a long junctional epithelium during periodontal wound healing: a review. J Periodontol. 1999 Dec;70(12):1511-22.

Lobmann et al, Expression of matrix-metalloproteinases and their inhibitors in the wounds of diabetic and non-diabetic patients. Diabetologia. 2002 Jul;45(7):1011-6. Epub 2002 May 25.

Pritchard et al, Simultaneous determination of follicle stimulating hormone and luteinising hormone using a multianalyte immunosensor. Analytica Chimica Acta, Volume 310, Issue 2, 30 June 1995, Pages 251-256.

Rowe et al Array biosensor for simultaneous identification of bacterial, viral, and protein analytes. Anal Chem. 1999a Sep 1;71 (17): 3846-52.

Rowe et al, An array immunosensor for simultaneous detection of clinical analytes. Anal Chem. 1999b Jan 15;71(2):433-9.

Maliszewska et al, Development of an ultrasensltive enzyme immunoassay for the determination of matrix metallopmteinases-9 (MMP-9) levels in normal human cerebrospinal fluid, J,

Neumimmunol. (2001): 116(2), 233-238. Chemical Abstracts, 7-Enzymes, Vol. 135, No. 16., 135:223205.

Silzel et al, Mass-sensing, multianalyte microarray immunoassay with imaging detection. Clin Chem. 1998 Sep;44(9):2036-43.

Sodek et al, Matrix metalloproteinases in periodontal tissue remodelling. Matrix Suppl. 1992; 1:352-62. Review.

Sorsa et al, Methods and test kits for specific and sensitive diagnosing of periodontal diseases. US5,736,341 Apr. 7, 1998.

Stratmann et al, MMP-TIMP interaction depends on residue 2 in TIMP-4. FEBS Left. 2001 Nov 2;507(3):285-7.

Taani et al An effective treatment for chronic periodontal abscesses. Quintessence Int. 1996 Oct;27(10):697-9.

Trengove et al Analysis of the acute and chronic wound environments: the role of proteases and their inhibitors. Wound Repair Regen. 1999 Nov-Dec;7'(6):442-52.

Vu et al Matrix metalloproteinases: effectors of development and normal physiology. Genes Dev. 2000 Sep 1;14(17):2123-33.

Wikesjo et al Periodontal wound healing and regeneration. Periodontol 2000.1999 Feb;19:21-39.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 82-96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sorsa et al, 1998 in view of Rowe et al, 1999 and further in view of Sodek et al, 1992. Sorsa et al teach a

method for detecting, in a sample of fluid from a chronic, periodontal wound, the matrix metalloproteinase-8 (MMP-8). The method of Sorsa et al uses an immuno-chromatographic lateral flow technique. An antibody to MMP-8 is coated onto particles and acts a label that can be detected, for example, by its fluorescent or chemiluminescent properties (col 13, parg 3). The label can be attached directly to the antibody (col 14, parg 4). In the method of Sorsa et al, a sample of gingival crevicular fluid from a patient with periodontal disease is applied to a reservoir of a capillary support/absorbent membrane system. The labeled antibody/particle, which is applied to the membrane, migrates by diffusion, coming in contact with and binding any MMP-8 in the sample. Further diffusion of the label/target antibody/particle/MMP-8 complex brings the complex into contact with a capture antibody that has been attached in a zone-like reaction site within the membrane. When the liquid flow carrying the complex migrates through this zone, label/target antibody/particle complexes that contain MMP-8 are bound to the reaction site zone via the capture antibody. Thus, the zone is detected if MMP-8 is present in the sample (Abstract; col 22, lines 19-45). A person of ordinary skill in the art would know that, since the process of migration occurs by diffusion, at the end of the membrane there is an area that collects buffer and reactants not bound to the reaction zone. The method of Sorsa et al uses antibodies that specifically recognize the active or proform of MMP-8 (col 10, parg 3; col 14, parg 4-5).

Sorsa et al do not teach a method for simultaneously detecting a plurality of metalloproteinases in a sample. Rowe et al teach a method for detecting a plurality of proteins in a mixed sample using an array comprising a plurality of capture antibodies specific for three different proteins (Fig 6). After incubation with the mixed sample, the binding of each specific protein to its respective capture antibody is detected by a fluorescently-labeled target antibody, which binds to the same specific protein. In this manner, the presence of each of a plurality of

proteins in a mixed sample is detected (Fig 4). Since the proteins in the mixed sample are separated, they can all be detected using either a single signal element (Fig 2) or different signal elements (Fig 6).

It would have been obvious to a person of ordinary skill in the art to incorporate the array approach of Rowe et al into the methods of Sorsa et al. In such a combined method, a sample of gingival crevicular fluid from a patient with periodontal disease, comprising a plurality of metalloproteases, would be reacted with particle-bound labeled antibodies specific for each protease. Then diffusion of the labeled-antibody-particle-metalloprotease complex would bring the complex into contact with an array of protease-specific capture antibodies, allowing detection of each specific metalloproteinase. Motivation to thus combine the methods of Sorsa et al and Rowe et al is derived from the fact that metalloproteases, including MMP-8 and MMP-9, are involved in periodontal disease (Sodek et al, 1992; Abstract, Figs 2 & 3). The combined method would support efficient determination of which proteases are present in patient samples for research analysis and/or clinical treatment. Therefore, Claims 82-96 are rejected under 35 USC 103(a) as being unpatentable over the combination of Sorsa et al, 1998 in view of Rowe et al, 1999 and further in view of Sodek et al, 1992.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claim 90 is rejected under 35 U.S.C. 112, first paragraph. The specification is enabling for identifying two or more metalloproteases in a mixed sample using a signal element unique

for each metalloprotease. The specification is also enabling for identifying two or more metalloproteases in a mixed sample using a single signal element wherein the metalloproteases are initially separated. However, the specification does not reasonably provide enablement for identifying two or more metalloproteases in a mixed sample using a single signal element wherein the metalloproteases are not initially separated. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate with these specific combination of steps and reagents, as is encompassed by this claim.

In regards to this enablement rejection, the application disclosure and claims are compared per the factors indicated in the decision In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but are not limited to: (1) the nature of the invention; (2) the breath of the claims; (3) the predictability or unpredictability of the art; (4) the amount of direction or guidance presented; (5) the presence or absence of working examples; (6) the quantity of experimentation necessary; (7) the relative skill of those skilled in the art. Each factor is here addressed on the basis of a comparison of the disclosure, the claims, and the state of the prior art in the assessment of undue experimentation.

Claim 90 is directed to a method of detecting two or more metalloproteinase in a mixed sample using a single signal element. The specification provides enablement for a method wherein the metalloproteases are initially separated, for example by gel electrophoresis, and then detected using a single signal element. However, Claim 90, as dependent from Claim 82, does not recite separation of the metalloproteinases prior to detection; both metalloproteinases are in

the same physical location and are to be detected with the same signal element. But, if both metalloproteases are in the same physical location and identified with the same label, how would the artisan know whether the mixed sample comprised the first metalloprotease, the second metalloprotease, or both metalloproteases? In fact, the artisan would not know. Neither the specification nor the prior art provides enablement for identifying two or more metalloproteases in a mixed sample, wherein the proteases are detected using a single signal element but are not initially separated. For these reasons, Claim 90 is rejected under 35 U.S.C. 112, first paragraph, for lack of enablement.

Written Description

Claim 90 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the Inventors, at the time the application was filed, had possession of the claimed invention. Claim 90 is directed to a method of detecting two or more metalloproteinase in a mixed sample using a single signal element. The specification describes a method, wherein the metalloproteases are initially separated, for example by gel electrophoresis, and then detected using a single signal element. However, Claim 90, as dependent from Claim 82, does not recite a method wherein the metalloproteases are initially separated prior to detection. The specification fails to describe how, if both metalloproteases are in the same physical location and identified with the same label, the artisan would know whether the mixed sample comprised the first metalloprotease, the second metalloprotease, or both metalloproteases. The specification teaches no representative species of such methods. Moreover, the specification fails to describe the method by any identifying characteristics or properties other than the functionality of being a means to

simultaneously detect a plurality of metalloproteases in a mixed sample using a single signal element, wherein the metalloproteases are not initially separated. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claim 90 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the Inventors, at the time the application was filed, had possession of the claimed invention. This claim is directed to a method of simultaneously detecting a plurality of metalloproteases in a mixed sample using a single signal element. Thus, Claim 90 encompasses the limitation of "wherein the first signal element and the second signal element are the same". Incorporating said limitation into a method of simultaneously detecting a plurality of metalloproteases, wherein the metalloproteases are not initially separated, introduces a new method into the claims. The specification fails to describe said method and, thus, Claim 90 is rejected under 35 U.S.C. 112, first paragraph, for introducing New Matter.

(10) Response to Arguments

Applicants' Arguments

I. Are Claims 82-96 rendered obvious by the combination of Sorsa et al, 1998, Rowe et al, 1999, and Sodek et al, 1992?

Appellants provide the following arguments in response to the rejection of Claims 82-96 under 35 U.S.C. 103(a) as being unpatentable over Sorsa et al, 1998 in view of Rowe et al, 1999 and further in view of Sodek, 1992.

I.(A) There is no motivation or suggestion to combine Sorsa et al and Rowe et al.

I.(A)(i) Sorsa et al do not teach a method for detecting a plurality of metalloproteases in a sample. In fact, Sorsa et al teach that MMP-8 is "the primary cause of gingival tissue destruction in periodontal disease (col 9, lines 47-53). Hence Sorsa et al teach that only MMP-8 need be detected in diagnosing periodontitis.

I.(A)(ii) Rowe et al does not include any mention of periodontal disease. None of the analytes detected by the method of Rowe et al are related in any way to one another. The method is directed to detecting different classes of analytes, none of which are related to periodontal disease or matrix metalloproteinases. Given the teachings of Sorsa et al, there is no reason for one to look to Rowe et al for additional information. Doing so is improper hindsight reasoning.

I.(B) There is no motivation or suggestion to combine Sorsa et al and Rowe et al with Sodek et al

I.(B)(i) Sodek et al examines the role of certain factors, including TGF-β, collagenase, gelatinase, and TIMP during the course of periodontal disease. Sodek et al does not mention any of the factors or methods of Rowe et al and fails to provide the requisite teaching, suggestion or motivation to combine the references as suggested. The teachings of Sodek et al are not relevant

I.(B)(ii) There is no reason to modify Sorsa et al in the manner suggested by the Office Action. Sorsa et al is clear in teaching that MMP-8 (collagenase) is the key member of the MMP group that involved in the progression of tissue destruction seen in periodontal disease (col 7, line 9-12).

Sorsa et al further teach that analysis of MMPs released due to non-periodontal conditions are a major problem in causing false positives and false negative results (col 4, line 51-55). Thus, Sorsa et al teach away from analyzing MMPs other than MMP-8.

I.(B)(iii) Neither Rowe et al nor Sodek et al provide motivation for ignoring the aspects of Sorsa et al that teach a method for detecting periodontal disease by analysis of MMP-8 only. In fact, Sodek et al agrees with Sorsa et al in asserting that it is collagenase that is the clear benchmark of periodontal disease (pg 354, col 1, lines 9-12 & col 2, lines 3-5 & 9-12).

I.(B)(iv) The proposed combination of Sorsa et al with Rowe et al and Sodek et al is improperly based on hindsight reasoning.

I.(C) Even if combined, the combination of Sorsa et al, Rowe et al, and Sodek et al fails to teach or suggest all of the limitation of Claim 82.

I.(C)(i) None of the cited references disclose or suggest the step of "collecting a sample from the fluid of a chronic wound". The Office Action asserts that Sorsa teach a method for detecting MMP-8 in a sample of fluid from a chronic, periodontal wound. Appellants disagree for the following reasons.

Chronic wounds are well known in the medical arts. Chronic wounds are produced by trauma or pathologic insult. Characteristics of chronic wounds include a loss of skin or underlying tissue. Examples include open cutaneous wounds, burns, neuropathic ulcers, pressure sores, venous stasis ulcers, and diabetic ulcers. Such a wound is neither disclosed nor suggested by Sorsa et al.

I.(C)(ii) A patentee can act as his own lexicographer. An explicit definition of a term will control interpretation of said term. Sorsa et al use the term periodontitis lesion in their patent and

includes a definition, wherein periodontitis lesion is synonymous with the term periodontitis pocket (col 2, lines 18-20; col 6, lines 8-12; col 12, lines 62-65).

Sodek et al describe periodontitis pockets as being caused by the downgrowth of the attached epithelium into the gingival crevice forming a pocket that provides an environment for pathogenic anaerobes. Said downgrowth, while providing protection to the underlying tissues, impairs regeneration and is the location of bursts of inflammation (pg 353, parg bridging col 1 & 2). Thus, the term "periodontitis lesion", as used by Sorsa et al and Sodek et al, is quite different from a chronic wound, as found in the claims under appeal. A wound is defined as, "an injury or damage, usually restricted to those caused by physical means with disruption of normal continuity of structures," (Evidence Appendix, 3) or, "an injury, especially one in which the skin or other external organic surface is torn, pierced, cut or otherwise broken," (Evidence Appendix, 5). The term 'chronic' is defined as, "persisting over a long period of time," (Evidence Appendix, 2), or, "of long duration; continuing; constant," (Evidence Appendix, 4). Thus, whether considering the accepted clinical definition of a chronic wound, as mentioned above, or combining the standard definition of "chronic" with that of "wound", a periodontitis lesion, as defined and used by Sorsa et al, is not synonymous with the term "chronic wound."

A periodontitis pocket is not an injury in which the skin or other external organic surface is torn, pierced, cut or otherwise broken and persisting over a long period of time, and it is not produced by trauma or pathologic insult. In addition a chronic wound involves completely different causes, biochemical pathways, treatments, and effects which are distinct from a periodontitis lesion. Thus, Sorsa et al does not disclose or suggest collecting a sample of fluid from a chronic wound, as is required in the claims under appeal.

The lack in Sorsa et al is not cured by Rowe et al or Sodek et al. No mention of any type of wound, pocket, lesion, or the like is found in Rowe et al. Sodek et al, while discussing periodontal pockets, similar to Sorsa et al, does not teach, suggest, or otherwise mention collecting a sample of fluid from a chronic wound.

Examiner's Response

I. Claims 82-96 are rendered obvious by the combination of Sorsa et al, 1998, Rowe et al, 1999, and Sodek et al, 1992.

I.(A) Reply: There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art (MPEP 2143.01). Thus, rejection of Claims 82-96 under 35 U.S.C. 103(a) as being unpatentable over Sorsa et al in view of Rowe et al and further in view of Sodek et al does not require that any one of these references explicitly teach or suggest the recited invention.

I.(A)(i) It is acknowledged that Sorsa et al does not teach a method for detecting a plurality of metalloproteases. In fact, if Sorsa et al did teach said method, Claims 82-96 would be rejected under 35 U.S.C. 102(b).

It is acknowledged that Sorsa et al states that MMP-8 activity is the primary cause of gingival tissue destruction in periodontal disease. However, the recited method is not a method for diagnosing periodontal disease. The recited invention is merely a method for detecting a plurality of proteases. Moreover, Sodek et al clearly teach that, in addition to collagenase (MMP-8), gelatinase activity (MMP-9) is also higher in periodontitis samples (pg 355, parg 2). Furthermore, Sodek et al state that, "These MMPs appear to be intimately associated with tissue destruction" (Abstract).

I.(A)(ii) It is not necessary for Rowe et al to mention periodontal disease or matrix metalloproteinases. The relevant teachings of Rowe et al are the technical aspects of analyzing a mixture of proteins using steps and procedures, which allow for the simultaneous detection of the proteins found in said mixture.

As described in the instant rejection, above, motivation to look to Rowe et al derives from the teachings of Sodek et al. Sodek et al teach methods for the independent, non-simultaneous detection of MMP-8 (Fig 2) and MMP-9 (Fig 3) in periodontal samples. Derived from said analysis, Sodek et al teach that MMP-8 and MMP-9 are "intimately associated with tissue destruction" during periodotitis (Abstract). The skilled artisan would know that a method for simultaneously detecting both MMP-8 and MMP-9 would be advantageous. Based on the nature of the problem to be solved, the skilled artisan would have looked to Rowe et al for the technical aspects of analyzing a mixture of proteins using steps and procedures, which allow for the simultaneous detection of the proteins found in said mixture.

I.(B) Reply: The three possible sources for a motivation to combine references are the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art.

I.(B)(i) Sodek et al teach independent, non-simultaneous detection of MMP-8 (Fig 2) and MMP-9 (Fig 3) in periodontal samples. Sodek et al conclude that MMP-8 and MMP-9 are "intimately associated with tissue destruction" during periodotitis (Abstract). The skilled artisan would know that a method for simultaneously detecting both MMP-8 and MMP-9 would be advantageous. Based on the nature of the problem to be solved, the skilled artisan would have looked to Rowe et al. Rowe et al teach the technical aspects of analyzing a mixture of proteins using steps and procedures, which allow for the simultaneous detection of the proteins found in

said mixture. Thus, the skilled artisan would have incorporated the technical aspects of Rowe et al, which allow for the simultaneous detection of the proteins found in a mixture, to solve the problem of Sodek et al. Thereby, a method would be devised for simultaneous detection of the MMP-8 and MMP-9 found in periodontal samples.

I.(B)(ii) It is acknowledged that Sorsa et al teach that MMP-8 is the primary cause of gingival tissue destruction in periodontal disease (col 9, parg 5). However, the elected invention is not directed to a method of diagnosing periodontal disease. Moreover, Sorsa et al teach that MMP-1, MMP-2, and MMP-9 are also implicated in periodontal disease based on the following. These proteases can be extracted from diseased tissue and are elevated in gingival crevicular fluid of periodontitis patients; in addition, the relative amounts of these proteases correlate with the severity of disease, decrease after treatment, and are induced in experimental models of periodontitis (col 6, parg 1). The skilled artisan would know that study of the biochemical processes involved in periodontitis would include examining the levels of MMP-1, MMP-2, and MMP-9. In addition, Sorsa et al teach detection of two forms of MMP-8, the active and proform. Thus, Sorsa et al teach detection of more that a single matrix metalloproteinase.

It is acknowledged that Sorsa et al teach that, because of the involvement of various host and bacterial-derived proteinase in the degradation of non-specific synthetic or natural substrates, such as gelatin, false negative and positive results occur (col 4, lines 51-55). However, the purpose of said discussion is to point out the pitfalls of activity-based assays in assessing periodotitis. Sorsa et al teach that activity-based assays have been developed for aspartate aminotransferase, β-glucuronidase, lactate dehydrogenase, arylsulfatase, elastase, and some general and trypsin-like proteinases (col 4, lines 1-18 and 32-45). They specifically state that the assays for gelatinase, elastase and general proteinase and trypsin-like proteinases activities lack

specificity, in part, because of the substrates used for analysis (col 4, lines 18-50). In this discussion, Sorsa et al do not mention analysis of MMPs or assert that analysis of MMPs, other than MMP-8, can lead to false positive and/or negative results in the diagnosis of periodontal disease. Thus, Appellants assertion, that analysis of MMPs release due to non-periodontal conditions are a major problem in causing false positive and negative results, are not consistent with said teachings of Sorsa et al.

I.(B)(iii) It is acknowledged that Rowe et al teach nothing specific to periodontal disease; the relevant teachings of Rowe et al are the technical aspects, which allow for the simultaneous detection of the proteins found in a mixture.

It is acknowledged that Sodek et al teach that increased MMP-8 activity correlates with the loss of tooth attachment and tissue distruction (pg 354, col 1, lines 9-12; col 2, lines 3-5 & 9-12). However, Sodek et al also teach that MMP-9 levels are elevated in periodontitis and are reduced after treatment (pg 355, parg 2), leading to the conclusion that MMP-9 is associated with tissue destruction (Abstract).

I.(B)(iv) The combination of Sorsa et al with Rowe et al and Sodek et al is based on the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art. The problem to be solved is to find an easy way to simultaneously detect a plurality of matrix metalloproteases in periodontal abscesses. Motivation to do so is derived from the teaching in the prior art that MMP-1, MMP-2, MMP-8, and MMP-9 are associated with periodontal disease (Sorsa et al; col 6, parg 1). The prior art also provides a technique for simultaneously detecting a plurality of proteins (Rowe et al). The skilled artisan would know that the technique of Rowe et al could be used to solve the problem of simultaneously detecting a plurality of matrix metalloproteases.

I.(C) Reply: The combination of Sorsa et al, Rowe et al, and Sodek et al teach and/or suggest all of the limitations of Claim 82.

I.(C)(i) Sorsa et al teach that, "Samples are collected preferably in a site-specific manner from gingival crevicular fluid associated with a specific site or lesion ... wherein the collecting is performed with a solid, absorbing sampling device" (col 11, parg 7-8).

Regarding periodontal disease being encompassed the term "chronic wound", the following is presented.

(a) The Merck Manual teaches:

Periodontal diseases inflame and destroy the structures surrounding and supporting the teeth, primarily the gums, the jawbones, and the outer layer of the tooth root. Periodontitis results from a long-term accumulation of plaque and tartar between the teeth and the gums. Pockets form between the teeth and gums and extend downward between the root of the tooth and the underlying bone. These pockets collect plaque in an oxygen-free environment, which promotes the growth of aggressive forms of bacteria. Plaque buildup irritates the gums, and they become inflamed. The early symptoms of periodontitis are bleeding gums. In time, the gums pull away from the tooth, creating a pocket that fills with more plaque. If the disease continues, eventually so much jawbone near the pocket is destroyed that the tooth loosens and could fall out. Periodontitis (pyorrhea) is a severe form of gingivitis in which the inflammation of the gums extends to the supporting structures of the tooth. Periodontitis is one of the main causes of tooth loss in adults and is the main cause in older people. Infection erodes the jawbone, which holds the teeth in place. The erosion weakens the attachments and loosens the teeth. An affected tooth may eventually fall out or need to be pulled out. Trench mouth, acute necrotizing ulcerative gingivitis, is a painful, noncontagious infection of the gums, causing pain, fever, and sometimes fatigue. Usually, trench mouth begins abruptly with painful gums, an uneasy feeling, and fatigue. Foul breath also develops. The tips of the gums between the teeth erode and become covered with a gray layer of dead tissue. The gums bleed easily, and eating and swallowing cause pain.

(b) Stedman's Medical Dictionary 27th Edition states:

Periodontitis 2. A chronic inflammatory disease of the periodontium occurring in response to bacterial plaque on the adjacent teeth; characterized by gingivitis, destruction of the alveolar bone and periodontal ligament, apical migration of the epithelial attachment resulting in the formation of periodontal pockets, and ultimately loosening and exfoliation of the teeth.

apical *p.* inflammation of the periodontal ligament surrounding the root apex of a tooth; usually a consequence of pulpal inflammation or necrosis.

p. complex vertical resorption of the alveolar process with pockets of uneven depth on adjacent teeth, and with traumatic occlusion as a factor.

Thus, periodontitis is defined as a chronic condition including inflammation, bleeding lesions, ulcerative necrosis, and/or traumatic occlusion. Based on said definitions, the skilled artisan would, more likely than not, interpret periodontitis as involving chronic wounds.

(c) Moreover, the prior art refers to periodontal disease in the context of chronic wounds.

See for example:

Taani et al, An effective treatment for chronic periodontal abscesses. Quintessence Int. 1996 Oct;27(10):697-9.

Bergstrom et al, Tobacco smoking and chronic destructive periodontal disease. Odontology. 2004 Sep;92(1):1-8. Review (esp Abstract).

Wikesjo et al, Periodontal wound healing and regeneration. Periodontology 2000; 19:21- 39 (esp pg 22, parg 1-2).

In addition, Graber et al, 1999 provide a review for the role of extracellular matrix proteinases in periodontal wound healing.

Graber et al, Role of interactions between integrins and extracellular matrix components in healthy epithelial tissue and establishment of a long junctional epithelium during periodontal wound healing: a review. J Periodontol. 1999 Dec;70(12):1511-22. Review.

Therefore, one of skill would know that the art discusses periodontal disease in the context of chronic wounds in which matrix metalloproteinases play a role.

I.(C)(ii) It is acknowledged that a patentee can act as his own lexicographer and an explicit definition with control interpretation. It is also acknowledged that Sorsa et al states that pockets >4mm are considered as periodontitis pockets or periodontitis lesions (col 2, parg 3). However, Sorsa et al fails to provide an explicit definition for periodontitis lesion that would substitute for what was known in the art; see (i) just above. In addition, Sorsa et al disclose: "Periodontal disease comprises a group of inflammatory disorders originating from infections affecting the gingiva (gum) and the alveolar (jaw) bone structures supporting the teeth. The

primary cause of periodontal diseases is bacterial plaque attached to the teeth. This causes inflammation of the gum which may result in destruction of the actual tooth-supporting structure and bone" (col 1, lines 21- 27). Sorsa et al further refer to "periodontitis lesions" (col 6, lines 8-9). Thus, Sorsa et al describe periodontal disease as a chronic condition comprising lesions and leading to destruction of the tooth-supporting structure and bone. Said chronic lesions and destruction certainly would be considered to be chronic wounds produced by "pathologic insult" including "a loss of skin or underlying tissue" and involving "neuropathic ulcers", as iterated by Appellants.

It is acknowledged that Sodek et al teach that periodontitis is accompanied by the downgrowth of the attached eptithelium in to the gingival crevice forming a pocket, a site of inflammatory activity (pg 353, parg 2). However, Sodek et al also teach that periodontitis includes ulceration of the epithelium and inflammatory lesions (Fig 1). The Examiner disagrees with Appellants' assertion that the term "chronic wound" would not encompass periodontitis lesions or necrosis as taught by Sodek et al. Periodontitis lesions or necrosis are produced by "pathological insult" and involve chronic "disruption of normal continuity" of gum structure, as iterated by Appellants.

The Examiner disagrees with Appellants' assertion that chronic wounds involve completely different causes, biochemical pathways, treatments, and effects, which are distinct from a periodontitis lesion. Armstrong et al, 2002 clearly teach that, as for periodontal disease, MMP-8 is the predominant collagenase in normal healing wounds and that elevated activity of said protease may be involved in the pathogenesis of nonhealing chronic ulcers (Abstract). Lobmann et al, 2002 teach that, as for periodontal disease, MMP-8 and MMP-9 are elevated in chronic diabetic wounds (Abstract). Thus, especially relevant to the instant application, the same

matrix metalloproteinases found in periodontal disease are also found in normal and ulcerative wounds.

It is acknowledged that Rowe et al does not discuss periodontal disease or chronic wounds. The relevant teachings of Rowe et al are the technical aspects of analyzing a mixture of proteins using steps and procedures, which allow for the simultaneous detection of the proteins found in said mixture.

Sodek et al do discuss collecting samples of crevicular fluid that exudes between the tooth and the gingival margin (pg 353, parg 3) and using samples of crevicular fluid collected in microcapillary tubes (pg 354, parg 1). Thus, Sodek et al do teach collecting a sample of fluid from a chronic wound.

For these reasons Appellants arguments are not found to be persuasive and Claims 82-96 are rejected under 35 USC 103(a) as being unpatentable over the combination of Sorsa et al, 1998 in view of Rowe et al, 1999 and further in view of Sodek et al, 1992.

Applicants' Arguments

II. Does Claim 90 fully comply with 35 USC 112, first paragraph?

II.(A) Claim 90 fully satisfies the enablement requirement of 35 USC 112, first paragraph.

II.(A)(i) The specification describes representative embodiments of methods encompassed by Claim 90 (Figs 1C, 3, & 4; pg 7, lines 3-15; pg 10, line 5 – pg 11, line 18). In one method, a sensor can include a plurality of fraction sites for simultaneous detection of more than one enzyme (pg 7, lines 3-15). Each reaction site contains a target antibody, which binds only one enzyme. Thus, no additional capture antibody is required to detect more than one enzyme.

In a second method, a fluid sample is exposed to a signal element and at least one target antibody that binds a target enzyme to form a complex. The complex is then captured by an immobilized capture antibody that binds the enzyme, which allows for localized detection.

Thus, representative embodiments use a capture antibody to separate and localize each target protease into reaction sites, wherein the capture proteases are visualized using a second protease-specific antibody labeled with a signal element.

II.(A)(ii) While the specification may not describe each and every method, in combination with what is generally known in the art, Claim 90 is enabled.

II.(A)(iii) The specification discusses the possibility of coupling the signal element and the target antibody to a particle (pg 8, lines 6-13). This embodiment is encompassed by Claim 89 and was encompassed by original Claims 18 and 20.

II.(A)(iv) Claims 18, 20, and 89 encompass yet another embodiment of the method of Claim 90, wherein one target antibody and the signal element are attached to a particle, while another target antibody and the signal element (i.e., the second target antibody of pending claim 82 and a target antibody encompassed in the 'at least one' language of original claim 18) are not attached to a particle. Identification of the two complexes either prior to or following detecting the signal element would have been well within the knowledge of one or ordinary skill in the art. Moreover, this particular embodiment of the invention of claim 90 can be carried out with no separation of the target proteinase enzymes necessary in order to establish the presence of the different metalloproteinases in the sample.

II.(B) Claim 90 fully satisfies the written description requirement of 35 USC 112, first paragraph.

II.(B)(i) The specification describes representative embodiments of a method encompassed by Claim 90 (Figs 1C, 3, & 4; pg 7, lines 3-15; pg 10, line 5 – pg 11, line 18).

II.(B)(ii) Methods encompassing the limitations of Claim 90 can be found in originally filed Claims 18-30. It is clear that said claims utilize only a single signal element, while detecting multiple enzymes using multiple target antibodies.

II.(C) Claim 90 does not introduce New Natter into the application.

II.(C)(i) The Final Office Action stated that the limitation "wherein the first signal element and the second signal element are the same," of Claim 90 introduced New Matter. The Advisory Action acknowledged that the specification teaches that a protease can be detected by exposing a sample to "a signal element" and at least one target antibody and that the same paragraph of the specification also states that such a method can be used to simultaneously detect more than one enzyme. However, the Advisory Action did not specifically state that the New Matter rejection was withdrawn. Appellants respectfully maintain that the content of the specification clearly indicates that the inventors invented and possessed the subject matter of Claim 90 as of the filing date of the application. Withdrawal of the rejection of claim 90 under U.S.C. §112, first paragraph, as failing to comply with the written description requirement, is requested.

Examiner's Response

II. Claim 90 does not fully comply with 35 USC 112, first paragraph.

II.(A) Claim 90 does not fully satisfy the enablement requirement of 35 USC 112, first paragraph.

II.(A)(i) The embodiments described by Figs 1C and 3 each encompass a sensor comprising a plurality of reactions sites, wherein "each reaction site can contain target antibodies

to only one proteinase enzyme" (pg 7, lines 3-15). Likewise, Fig 4 describes and embodiment encompassing a sensor comprising a plurality of reactions sites, wherein "each reaction site has different capture antibodies bindable to only one proteinase enzyme" (pg 10, lines 35-36). Thus, the sensors of Figs 1C, 3, and 4 are used in methods of separating proteinase enzymes into reaction sites for detection. In each of these embodiments, since the proteinase enzymes are separated into reaction sites, the skilled artisan would know that the method could use a single signal element. As explained in the rejection, above, such embodiments satisfy the enablement requirement.

For example, the following is taught by the specification for the embodiment of Fig 4 (parg bridging pg 10-11).

> The sample from the chronic wound is added to the sample chamber of a sensor, which contains polystyrene beads coated with target antibodies and a dye (signal element). If a proteinase enzyme is present in the chronic wound fluid, it will bind to a specific target antibody and form an enzyme/target antibody-signal element complex. The sample containing the complex flows to the reaction sites, the location of specific capture antibodies. Each reaction site has a different capture antibody, which binds only one proteinase enzyme. Capture antibodies bind to the proteinase enzyme present in the complex and, thus, bind the complex to form a conjugate. Protease-specific conjugates are held in the reaction site and any complexes that did not bind to the first reaction site flow to the next reaction site where the same process takes place. Thus, each reaction site binds a protease-specific complex comprising a single, common signal element. The conjugate formed in each reaction site results in an increasing concentration of beads containing the dye molecule (signal element). The concentration of beads held by the conjugate causes a detectable manifestation of the signal element, such as the presence of a color. The presence of color in sites 20, 21, 22, 24, and 25 indicate the presence of MMPs 1, 8, 9, and pro-MMP1 respectively.

Thus, the method of Fig 4 can use a single signal element because the proteases are separated into distinct reaction sites. The methods of Figs 1C and 3 can also use a single signal element because the proteases are separated into distinct reaction sites.

II.(A)(ii) Neither the specification nor the prior art provide any example or guidance on how to detect a plurality of metalloproteases using a single signal element, wherein the metalloproteases are not separated.

II.(A)(iii) It is acknowledged that the specification teaches the possibility of coupling the signal element and the target antibody to a particle (pg 8, lines 6-13). Moreover, the specification teaches use of such a particle in the embodiment of Fig 4 (parg bridging pg 10-11; see (i), just above). It is also acknowledged that use of such a particle is encompassed by Claim 89, as well as original Claims 18 and 20. However, coupling the signal element and the target antibody to a particle does not solve the problem of how to detect a plurality of metalloproteases using a single signal element, wherein the metalloproteases are not separated.

II.(A)(iv) The instant argument appears to assert the following. The use of a method to detect two proteases within a mixture, wherein the first protease is bound, via an antibody, to a signal element-labeled particle, while the second protease is bound to a signal element-labeled antibody but not a particle. Appellants assert that the two complexes within the mixture could, thus, be detected with no separation of the two proteases.

This argument is not found to be persuasive for the following reason. Under the described conditions, there is a single signal element. Within the mixture, both the first protease (particle-bound) and the second protease (non-particle bound) are labeled with the same signal element. Any technique for detection will detect that one signal element, regardless of whether it is bound to the first protease, via the particle, or bound to the second protease. The skilled artisan would know that it would be impossible to differentiate between the two signal element-labeled proteases in the mixture. The skilled artisan would know that in order to differentiate between the two proteases, both labeled with the same signal element, the two proteases must be

separated. Therefore , the described method has no means to differentiate between the two proteases.

Thus, Claim 90 is rejected under 35 USC 112, first paragraph, for lack of enablement.

II.(B) Claim 90 does not fully satisfy the written description requirement of 35 USC 112, first paragraph.

II.(B)(i) As explained above in Section II(A)(i), each of the embodiments described in Figs 1C, 3, & 4 as well as in the specification at page 7, lines 3-15 and page 10, line 5 – page 11, line 18, encompass separating proteinase enzymes into reaction sites and, thus, the embodiments can use a single signal element for detection.

II.(B)(ii) Claim 18, by reciting the use of a "capture antibody" (lines 1–11) encompasses separation of the proteinase enzymes. Claims 19-25, as dependent from Claim 18, also encompass separation of the proteinase enzymes.

Claims 26-30 were not encompassed by the elected invention. Nonetheless, Claim 26, in reciting the use of a "capture antibody" (lines 10–11) encompasses separation of the "a least one proteinase enzyme" (lines 12-13). Claims 27-30, as dependent from Claim 26, also encompass separation of the "a least one proteinase enzyme".

Thus, Claim 90 is rejected under 35 USC 112, first paragraph, for insufficient written descripiton.

II.(C) Claim 90 introduces new matter into the application.

II.(C)(i) The specification, at page 10, parg 2, describes one aspect of the invention. As explained in the Advisory Action of September 1, 2006, certain limitations of said aspect include "a signal element" and "at least one target antibody". However, said aspect also specifically recites the use of a "capture antibody" which "is attached to the surface of a reaction site" (pg 10,

lines 14-15). Moreover, said aspect states that, "Ideally, capture antibodies for one target proteinase enzyme are placed in each reaction site". Thus, said aspect encompasses separation of the proteases in the mixture for detection by a single signal element.

Neither the specification nor claims, as filed, disclose a method for detecting a plurality of proteases using a single signal element, wherein the proteases are not separated by capture antibodies. Thus, Claim 90 is rejected under 35 USC 112, first paragraph, for introducing New Matter.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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